REMARKS

Claim 33 has been amended to limit the particulate delivery vehicles to liposomes and accordingly claim 35 has been canceled. This is not, of course, new matter as the possibility of liposomes was already listed in claim 35.

Claim 33 has also been amended to clarify that the first composition is administered together with the second composition. This is supported in paragraph 84, which describes the construction of a kit wherein the compositions are premeasured for separate administration at the same time.

Claim 33 has also been amended to clarify that the ratio of fluoropyrimidine and the water soluble camptothecin administered is synergistic; this limitation was present in claim 33 as originally presented and thus does not constitute new matter.

Claim 34 has been amended simply to conform and to clarify that 4.5 refers to nanometers.

Claims 43 and 44, that were withdrawn from consideration have been canceled.

Obviousness

There is only one outstanding ground for rejection which is applied to all claims. This rejection is made for asserted obviousness over the combination of WO01/62235 (WO01) in view of WO95/15154 (WO95), U.S. 7,122,553 (Rahman) further with Vaage, *et al.* (*Int. J. Cancer* (1993)) and Mayer (6,083,530). Applicants are not entirely clear of the meaning of "by themselves or in combination" at the end of the sentence as this appears inconsistent with the preceding portions of the sentence. Applicants are assuming that the rejection is made over the combination of these documents.

WO01 is said to disclose separate administration of camptothecin and a pyrimidine derivative in a manner in which therapeutic synergy is achieved. It is noted that not all of the pyrimidine derivatives are fluoropyrimidines, *e.g.*, uracil, and the exemplified pyrimidine derivative, capecitabine, which is no longer a fluoropyrimidine as it lacks a pyrimidine ring (page 6).

Respectfully, WO01 is missing much more than liposomes. First, the definition of synergy as set forth in this document is completely different from that required by the present claims. As noted in the papers filed in connection with the parent application herein (U.S. Serial No. 10/817,735), the definition of synergy in this document is on page 4 at lines 15-18. According to this definition, a combination manifests therapeutic synergy if it is therapeutically superior to one or the other of the constituents used at its optimum dose. That definition contradicts the requirements of the present application. The present application requires that the synergy is such that the combination is greater than additive. The requirement for at least additivity in the present application is set forth on page 12 at the beginning of paragraph 49. Thus, if the optimum dose of component A is 5 and the optimum dose of component B is 7, a combination of these optimum doses must be greater than 12. According to the definition in the cited document, the combination would be synergistic even if it only yielded an efficacy of 8.

In addition, WO01 does not require that the ratio of the fluoropyrimidine and the water soluble camptothecin administered be synergistic. It further does not require that this ratio be maintained which is, indeed, the purpose of including these agents in liposomes in the present invention.

So WO01 differs from the requirements of claim 33 in the following ways: It does not encapsulate either drug in liposomes, it does not require administering a synergistic ratio of any kind, and the criterion for any synergy that might be achieved does not relate to the same synergy that is required by the invention. Most important, there is no disclosure in WO01 that any administered synergistic ratio is maintained for at least an hour.

As to the dependent claims, the limitations of claims 39-42 are also not suggested by this document.

WO95/15154 is cited because it discloses treatments using 5-FU entrapped in liposomes. However, the combination of this document with WO01 fails to suggest the invention because it fails to require that the liposomes be carriers for both drugs and that the liposomes be such that the synergistic ratio administered be maintained for at least one hour in the subject.

Rahman is cited as teaching liposomal compositions containing irinotecan for assertedly increased therapeutic efficacy and reduced toxicity. Even if Rahman is combined with the foregoing two documents, it fails to teach the essential feature of the invention – that a synergistic ratio administered must be maintained for at least one hour in the blood of a subject after administration. The whole point of the invention is to do this. There is no teaching in any of the documents that the liposomes should be designed in such a way that any synergistic ratio administered is maintained.

This set of documents is then combined with Vaage which describes administration of two separate liposome formulations. Liposomes containing doxorubicin (Doxil®) and vincristine (S-VCR) are said to show improved therapeutic efficacy as compared to these drugs not encapsulated in liposomes. However, co-administration of these compositions according to Vaage

shows deleterious effects. Figure 5 plots tumor volume against time under various protocols. Line 6, which represents simultaneous Doxil® and S-VCR treatment, shows higher tumor growth than line 3 which represents the administration of Doxil® alone. Only by alternating the administration of Doxil® and S-VCR are improved results seen. In these cases, the first drug was given on days 3, 10 and 17 and the second drug on days 6, 13 and 20. Thus, any improved effects by virtue of combination treatment is achievable only by alternative dosing regimens, not by maintaining a synergistic ratio that is administered. Vaage could show an improved effect of the combination of drugs only by altering the times of administration of each component of the system, as opposed to their administration together as required by the present claims.

Finally, the Office cited Mayer in column 9, lines 20-25, which indicates that "drug cocktails" may comprise two or more populations of liposomes containing drugs. But, there is nothing in Mayer that would imply that the ratio of the components in the cocktails be set so as to be synergistic in the first place, much less any suggestion that the liposomal formulations be adjusted to control the pharmacokinetics so that the ratio is maintained.

The Office then draws the conclusion that to administer the camptothecin and pyrimidine derivatives of WO01 in liposomes would have been obvious. Perhaps so. That is not the invention. Claim 33 and its dependent claims demand much more than this. These claims demand that a synergistic ratio of the drugs, as defined in the present application, be administered, which, the Office is reminded, is quite different from the synergistic effect defined by WO01. Second, and critical, is the drugs be associated with the liposomes in such a way that the synergistic ratio of the drugs is maintained in the blood for at least one hour. There is no document that suggests this limitation.

In summary, the invention is based on the understanding, unique to the disclosure herein, and required by the claims, that in combination therapy, the drugs in the combination must have a greater than additive effect on the target tumor cells and that therefore a ratio of drugs that has been shown to have such a greater than additive effect must be administered. Not only must such a ratio be administered, but it must be maintained, and it can be maintained by preparing the compositions in such a way that the pharmacokinetics of the drugs are controlled by liposomes. The ratio administered is thus maintained at least for one hour in blood. There is no suggestion or hint of this basic concept that underlies the invention in any of the documents cited whether taken individually or taken together. The invention does not lie in administering two drugs in liposomes. The invention lies in providing liposomal compositions that contain a synergistic ratio of the drugs and that maintain a synergistic ratio of the drugs after administration to the subject. Where, in any of the documents, does even a hint of this concept appear?

The examples in the present application clearly demonstrate the importance of the invention concepts to efficacy. As shown in Example 5, liposomes containing FUDR and CPT-11 at a 1:1 ratio were encapsulated in liposomes (DSPC/DSPG/CHOL 7:2:1 mole ratio) and injected into mice (paragraphs 113-114). Figures 6A and 6B show the results. Figure 6A contrasts the ratio obtained when the same ratio is administered as a free drug cocktail as compared to the liposome encapsulated drug combination. The free drug cocktail drug ratio drops essentially 10-fold within minutes while the combination administered in liposomes is maintained for 24 hours at least. The efficacy of two types of administration was contrasted in Example 7, specifically in paragraphs 124-125 with the results shown in Figures 8A and 8B. As shown in Figure 8A, tumor growth was significantly inhibited only when the liposomal formulation that maintains the

synergistic ratio was administered; the results being dramatically better even than higher dosage levels of the free drug combination. These results are confirmed in Figure 8B for a different type of tumor.

Only the inventors herein recognized that combination therapy should be designed so that the combination of drugs is administered as a ratio where the effects of the drugs are more than additive and only the inventors herein recognized that that ratio must be maintained once administered by controlling pharmacokinetics using liposomes. There is absolutely nothing in the cited documents that suggest anything more than simply putting drugs into liposomes. The essence of the invention is missing from these documents. Accordingly, this basis for rejection should be withdrawn.

Double-Patenting

The pending claims were rejected as putatively double-patenting over certain claims in co-pending applications 10/817,735; 11/304,328 and 10/553,373. A terminal disclaimer with respect to these applications is submitted herewith.

Conclusion

The claims have been amended so as more particularly to point out the invention. The invention resides in administering, together, two compositions containing two different drugs where the administered ratio is synergistic and the ratio is maintained *in vivo* by virtue of stably associating the drugs with liposomes that control the pharmacokinetics to maintain the ratio for at least one hour. None of the documents cited by the Office alone or together suggest this concept.

Double-patenting rejections have been addressed by terminal disclaimer.

Therefore, applicants believe claims 33-34 and 36-42 are in a position for allowance and passage of these claims to issue is respectfully requested.

Should minor points remain that could be resolved by phone, a telephone call to the undersigned is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 532552000701.

Respectfully submitted,

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